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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,659	07/20/2000	Tommy Abrahamsson	1103326 0629	9094

7590 12/07/2004

White & Case
Patent Department
1155 Avenue of the Americas
New York, NY 10036-2787

EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,659	ABRAHAMSSON ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9,11-17,19-23,25,26,28-33,41,42,47,54 and 61* is/are pending in the application.

4a) Of the above claim(s) *3,9,11-17,19-23,25,26,28-30,32,33,47,54 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4-8, 31, 41, 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/8/04 has been entered.

Pursuant to the directives of the response filed 11/8/04, claims 2 and 3 have been amended. Claims 2-9, 11-17, 19-23, 25, 26, 28-33, 41, 42, 47, 54, 61 remain pending, of which claims 3, 9, 11-17, 19-23, 25, 26, 28-30, 32, 33, 47, 54, 61 remain withdrawn from consideration. Claims 2, 4-8, 31, 41, 42 are examined in this Office action.

Applicants' arguments filed 11/8/04 have been considered and found persuasive in part. The rejection of claim 2 over Eisenbach-Schwartz ('939) in view of Watson ('386) is withdrawn, as is the rejection of claim 2 over Eisenbach-Schwartz ('939) in view of Franson ('510).

Applicants have requested rejoining of the "kit" claims and the method claims. However, even apart from the issue of novelty, these claims (drawn to kits and methods) encompass a non-elected invention (claim 3). It is suggested that the "kit" claims and method claims be amended to delete reference to claim 3; this will facilitate continued prosecution of the application.

As indicated previously, the abbreviation "CPU" hereinbelow refers to carboxypeptidase

U.

✧

Claims 2, 4-8, 31, 41, 42 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of claims 4-8, 31, 41, 42 is dependent on non-elected claim (claim 3).
- Claim 2 makes reference to a "derivative" of a thrombin inhibitor. What are the limits here? For example, would a single amino acid or functional group be encompassed?
- In claim 8, the qualifier "about" renders the claim indefinite as to the upper and lower limits of the range. For example, would the ratio 1050:1 be encompassed?
- Claim 31 is indefinite as to the intended diseases. For example, are Alzheimer's disease, atherosclerosis and septic shock included?
- In claim 42, the qualifier "about" renders the claim indefinite as to the upper and lower limits of the range.

✧

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 4, 5, 8, 41, 42 are rejected under 35 U.S.C. §103 as being unpatentable over Eisenbach-Schwartz (USP 6,126,939) in view of Watson (USP 6,326,386); or Eisenbach-Schwartz (USP 6,126,939) in view of Franson (USP 6,020,510).

Eisenbach-Schwartz discloses (col 3, line 38) that the dipeptide Arg-Glu can be used to treat various inflammatory disorders, such as those recited in cols 5-6 of the reference. This compound is encompassed by formula II of claim 3 when the substituent variables correspond as follows:

R7 = C_4-alkyl substituted with two basic groups
X = -CO-NH-
Y = $-CH_2-$
R8 = hydrogen
R9 = -COOH
R10 = -COOH

Applicants have argued that since claim 2 has been amended to exclude the peptides disclosed by Eisenbach-Schwartz, the rejection of claims 4, 5, 8, 41, 42 has been overcome.

However, each of these claims (claims 4, 5, 8, 41, 42) is dependent on claim 3. Although claim 3 is drawn to a non-elected invention, the cited claims are still dependent on claim 3; accordingly, the rejection is maintained.

✧

Claims 2, 4, 5, 8, 41, 42 are rejected under 35 U.S.C. §103 as being unpatentable over Ondetti (USP 4,177,277) in view of Watson (USP 6,326,386).

As indicated previously, Ondetti discloses (col 3, line 18+) compounds that are useful to treat cardiovascular conditions and inflammatory conditions. The compounds can also be used (col 7, line 57) to treat oedema. The following compound is disclosed by Ondetti, and would be encompassed by claim 2 if this claim permitted R1 to be aminopropyl:

R1 = aminopropyl
X = $-CH_2-$
Y = $-CH_2-$
R2 = hydrogen
R3 = -COOH
R4 = -SH

As it happens, claim 2 now excludes the possibility of R^1 being aminopropyl. However, claim 2 does not exclude R^1 being aminobutyl. While the possibility of variable "m" (of Ondetti) representing the integer 5 is not stated in the reference, the medicinal chemist of ordinary skill would have regarded a compound containing aminobutyl to be an "obvious

variant" of an otherwise identical compound containing aminopropyl. That is, the two compounds in question are close homologs differing only in the presence of one methylene group. The medicinal chemist of ordinary skill would have expected, *a priori*, substantially identical activity for the two homologs. [*In re Shetty* (**195** USPQ 753) and *In re Hass & Susie* (**60** USPQ 544)].

In response to the foregoing, applicants have argued that the compound cited by the examiner cannot have any biological activity because Ondetti asserts that it is a synthetic intermediate. Applicants are thus arguing that a single compound cannot have more than one property. This assertion is clearly untrue, but in any case, Ondetti asserts that the compound at issue can be used in each of two different ways. First, it can be used as a synthetic intermediate. But in addition to this, it can also be used to treat cardiovascular conditions and inflammatory conditions. Ondetti, in fact, explicitly states (e.g., col 3, line 14+) that the compound can be used in each of two different ways. The fact that the compound may also be used to synthesize other compounds does not in any way detract from its use as a therapeutic agent. On the other hand, if applicants have evidence that the compounds of Ondetti are ineffective in the treatment of cardiovascular and inflammatory conditions, applicants may present such evidence and it will be considered.

Applicants have argued that it is "inappropriate" to assume that the compound in which R1 is aminobutyl will be inactive, while at the same time, the compound in which R1 is

aminopropyl is active. However, this runs contrary to what is recognized by medicinal chemists, and the Courts. On the other hand, if applicants have evidence that the compound of Ondetti is ineffective (in the treatment of cardiovascular and inflammatory conditions) when R1 is aminobutyl, applicants may present evidence of the same. Barring the presentation of such evidence, however, the case for prima facia obviousness is on firm ground.

. . . .

Applicants have also made reference to Hashimoto (*Thrombosis and Haemostasis*, 2002, 87:110-113) and Latacha (*Journal of Thrombosis and Haemostasis*, 2003, 128-134). Applicants have argued that these references support the contention that the claims are "enabled". However, the examiner has not argued lack of enablement of the pending (and elected) claims. There is no need to debate the merits of a rejection that has not been imposed. The issue instead is that of "unexpected results", and more to the point, the issue of the extent to which the "unexpected results" might outweigh the finding of obviousness, or *vice versa*. The Hashimoto and Latacha references do not support an assertion of "unexpected results"; any such assertion can only be based on the data provided in the specification (as least that is true based upon the record thus far).

On the subject of "unexpected results", applicants have argued (pages 18-19, response) that if an oncologist reviewed the data in tables I, II and III of the instant specification, and

found the results to be "unexciting", the fact of this would not be material to the issue of patentability of the instant claims. The examiner would concur with applicants on this particular point. Next, applicants have argued that if an oncologist reviewed the data in tables I, II and III of the instant specification, and found the results to be irrelevant to his own work, the fact of this would not be material to the issue of patentability of the instant claims. This particular point will be left unchallenged at the present time. Next, applicants argue the following:

> "…The Examiner opines that various uses are suggested which have little relevance to the 'unexpected results' that were obtained. The uses particularly singled out by the Examiner are the treatment of Alzheimer's disease, atherosclerosis and septic shock. … [The specification discloses] a nexus that unites these and other diseases as candidates for treatment with the mixture of inhibitors that is the instant invention."

This reference to a "nexus" might be appropriate if an enablement rejection been imposed. But this is not the case. The examiner does not argue that any of claims 2, 4-8, 31, 41 or 42 lacks enablement. Rather, the issue is that of obviousness *versus* "unexpected results". In addressing this issue, it is appropriate to consider various compounds that might fall within the scope of the claimed genus, and various ways of using those compounds (in accordance with teachings in the specification). In particular, this ground of rejection focuses on thrombin inhibitors that were not disclosed in the specification, and on treatment of diseases for which no "unexpected results" have

been provided. As stated previously by the examiner, if the artisan of ordinary skill is intent on treating Alzheimer's Disease or atherosclerosis or septic shock (for example), he is unlikely to be concerned about the degree of inhibition of fibrin deposition in the lungs. Thus, for treatment of a disease in which fibrin deposition in the lung does not occur, the results presented (tables I – III, specification) are not especially "unexpected". Applicants have raised the question of relevance of cancer treatment to the claimed invention. Whether cancer is relevant or not, the fact remains that treatment of Alzheimer's Disease, atherosclerosis and septic shock are relevant, since applicants have argued in the specification that they are relevant.

Thus, the results (tables I – III, specification) are not sufficiently "unexpected" to overcome the obviousness rejection, at least for those thrombin inhibitors which have not been disclosed in the specification, and especially when the compositions are being used to treat a disease for which fibrin deposition in the lungs is not relevant.

The rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600